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Effects of Amphetamine and β -Endorphin Fragments on Maze Performance in Rats

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DE BOER, S. AND B. BOHUS. *Effects of amphetamine and β -endorphin fragments on maze performance in rats.* PHARMACOL BIOCHEM BEHAV 36(3) 555-561, 1990. — Fragments of β -endorphin and amphetamine cause similar effects in some tests of maze behavior in rats. The present study served to compare the influence of amphetamine and two β -endorphin fragments [β -endorphin (β E)-(2-9) and β E-(2-16)] on maze behavior in more detail. In Experiment I no significant effects of amphetamine and the peptides on behavioral performance in three selected Davenport configurations were found. In Experiment II amphetamine increased the frequency of errors and of returns to the start box, but only in the first trial. This effect was dependent on the rats' experience and on the maze configuration. In the next 11 trials, amphetamine slightly decreased the overall frequency of errors and of returns to the start box. Therefore, the effects of amphetamine on maze behavior depend upon the extent of training experience and on the structure of the test mazes. The peptides did not significantly affect maze performance. It is concluded that the effects of amphetamine and the β -endorphin fragments on maze behavior are not comparable in this maze test.

Rat maze behavior β -Endorphin-(2-9)	Hebb-Williams mazes β -Endorphin-(2-16)	Amphetamine	α -Type endorphins	β -Endorphin fragments
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BETA-ENDORPHIN [β E-(1-31)] and its fragments influence rat behavior in various experimental situations. Effects have been found on, e.g., active and passive avoidance behavior (2, 7-9, 11), habituation (11), exploratory and social behavior (15) and maze behavior (2,12). Some of these actions appeared to be similar to those of morphine, while others were different from "classical" opiate-like influences. One group of beta-endorphin fragments which show behavioral effects through nonclassical opioid mechanisms is that of the α -type endorphins, which consists of α -endorphin [β E-(1-16)] and its fragments, e.g., β E-(2-16), β E-(1-9) and β E-(2-9). Their behavioral effects resemble those of amphetamine in a number of respects. Amphetamine as well as the α -type endorphins delay the extinction of pole jump behavior, facilitate passive avoidance behavior, increase substantia nigra self-stimulation and attenuate the grasping response of rats with lesions of the parafascicular area of the thalamus (10, 19-21). The peptides also enhance the apomorphine-induced stereotyped sniffing (20). In a series of food-rewarded problem solving experiments in Hebb-Williams type of mazes, amphetamine, β E-(2-9) and β E-(2-16) increased the number of errors (2). The resemblance between the effects of amphetamine and α -type endorphins on rat behavior may mean that these substances work through at least partly similar mechanisms. Therefore, we were interested in a further comparison of the behavioral effects of amphetamine and α -type endorphins.

Hebb-Williams type mazes were selected as a test situation. They have the advantage that drug effects on different aspects of the behavioral functioning can be picked up easier, because the test scores may be influenced by more than one process, e.g.,

changes in learning capacity, exploration, locomotor activity or motivation. However, because the behavioral changes leading to changes in error scores may be complex, it is necessary to analyze the behavioral changes into more detail if an effect is found. In previous experiments Bohus (2) found an increased number of errors in rats treated subcutaneously with 0.45 mg/kg amphetamine, 0.125 mg/kg β E-(2-9) and 0.125 mg/kg β E-(2-16) one hour before the test sessions in three Rabinovitch-Rosvold (16) configurations. No further analysis of the underlying behavioral changes was performed. Therefore, it is possible that the behavioral effect of the endorphins was different from that of amphetamine, even though the resulting changes in error score were similar. In a subsequent experiment (5), rats treated with 0.125 mg/kg β E-(2-16) one hour before the test sessions showed a decreased number of errorless trials in a series of 12 Davenport configurations (4). This effect was most pronounced in T3 and T9 of the series, and absent in T1. Thus, the effect may be configuration dependent. In order to shorten the long series of 12 configurations, we selected T1, T3 and T9 for further comparative study of effects of amphetamine and two α -type endorphins, β E-(2-9) and β E-(2-16) (Experiment I).

In a second experiment (II) the same compounds were tested as in Experiment I. However, the experimental procedure was changed in such a way that eventual interactions of the drug effects with test configuration and with maze running experience of the rats could be detected. The animals were tested on two test days with an interval of seven days on which they were trained further in different configurations without treatment. Therefore, the drug effects were tested in a relatively early and a relatively late phase

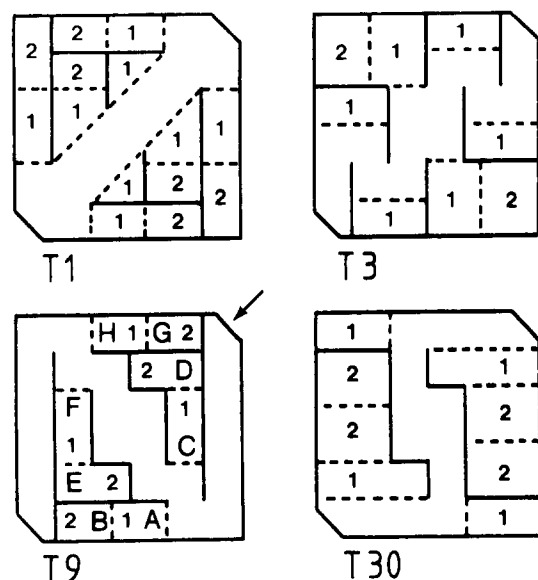


FIG. 1. The test configurations used in the experiments. Dotted lines indicate the limits of the error zones. 1 = first error zone, 2 = second error zone. The letters in the blind alleys of T9 correspond to those in Table 1. The arrow above T9 indicates the place of the start box for the calculation of the error patterns. For all configurations the start/goal boxes are situated in the upper right and lower left corner of the maze.

of the experiment, resulting in two clearly different levels of maze running experience. On each of the two test days two different maze configurations were used, half of the rats were tested in T9 of the Davenport series and the other half were tested in a newly designed configuration T30. Rats were always tested in different configurations on the two test days. T9 from the Davenport series was selected because in this configuration an effect of β E-(2-16) has been found previously. T30 is a symmetrical configuration (so that rats could run in two directions like in the Davenport configurations) with spatial characteristics related to those of the Rabinovitch-Rosvold series, in which more pronounced effects of amphetamine and α -type endorphins were found (2) than was the case in the Davenport series. The Rabinovitch-Rosvold configurations have smaller numbers of blind alleys with relatively large areas compared to the Davenport configurations. These properties seem to lead to larger numbers of errors per alley (6). The different types of configurations may test different aspects of the rats' maze running abilities and therefore also be differentially sensitive for detection of drug effects on maze behavior.

METHOD

Animals and Housing

Male Wistar rats were housed 4 per cage. Experiments were performed in the light phase (light on: 0530–1930 hr), each day at about the same time. Water was supplied ad lib.

Food Deprivation Schedule

Immediately after the habituation sessions the food was taken away. Food was supplied after each pretraining or test session, immediately after the return of the last rat to the cage, for a period of 90 minutes. From Friday until Sunday morning food was given ad lib, no training or testing was performed in the weekend. On this deprivation scheme the body weights of the animals were reduced to about 80–90%.

Drugs and Injections

β E-(2-9), β E-(2-16) (Organon International BV, Oss, The Netherlands) and d-amphetamine sulfate (OPG, Utrecht, The Netherlands) were dissolved in 0.9% NaCl, which also served as the control solution. The doses were equal to those shown to be effective in earlier studies (2). Injections were always given subcutaneously (SC) in a volume of 0.5 ml/rat, 60 min before the test session (which was the same treatment-test interval as in previous studies).

Apparatus

The maze was constructed after the description of Davenport and co-workers (4). The field was 60 × 60 cm, with end (= start/goal) boxes of 18 × 38 cm, walls of 20 cm high, and barriers of 10 cm high. Sliding doors separated the end boxes from the field. The whole apparatus was covered by wire mesh right above the barriers in the field, and above the walls of the end boxes. Food pellets were dropped into two dishes (diameter 5 cm), one in each end box. The only light source in the experimental room was a 40-W dim bulb fixed at a distance of 1 m above the centre of the bottom of the field of the maze.

Training and Testing

On the first day the rats were habituated by means of two 5-min exploration sessions (separated by at least 1 hour) in the maze without barriers, starting once from each of the two end boxes. Subsequently, the animals were pretrained in 5 different simple configurations, P1–P5 (6), and tested in more complex configurations. Throughout pretraining and testing one session per day was given, with 12 trials per session, and intertrial intervals of 15 sec. The two end boxes served alternately as start and goal box. Reward consisted of two 45-mg Noyes pellets per trial. Animals that refused either to leave or to enter start- or goal-box or to eat in the pretraining phase, were discarded, as well as animals with a total running latency of 360 sec or longer in P5.

Behavioral Measures

Behavioral measures were: (A) The number of first zone errors (frequency of entering error zones marked with a 1 in Fig. 1). (B) The number of second zone errors (frequency of entering error zones marked with a 2 in Fig. 1). (C) The number of start box visits (the number of times a rat re-entered the start box with 4 paws). (D) The number of errorless trials per session (the number of trials per session in which no errors were made). (E) The error pattern. The distribution of errors over the different error zones and its change in the course of the session were determined. For each trial the number of rats that visited a particular error zone at least once, was expressed as a percentage of the total number of rats in the corresponding treatment group (pattern of initial errors). In the same way for each particular error zone the percentage of rats per group that visited it at least twice was determined (pattern of repeated errors).

Statistical Analysis

Because of heterogeneity of the data, two nonparametric statistical tests were selected: the Kruskal-Wallis test, in case of significance followed by the Mann-Whitney U-test (3), and the k-sample test for aligned observations for unequal-sized samples (14). For all tests a significance level of 0.05 was used. Pairwise comparisons of groups were two-tailed, and were performed only

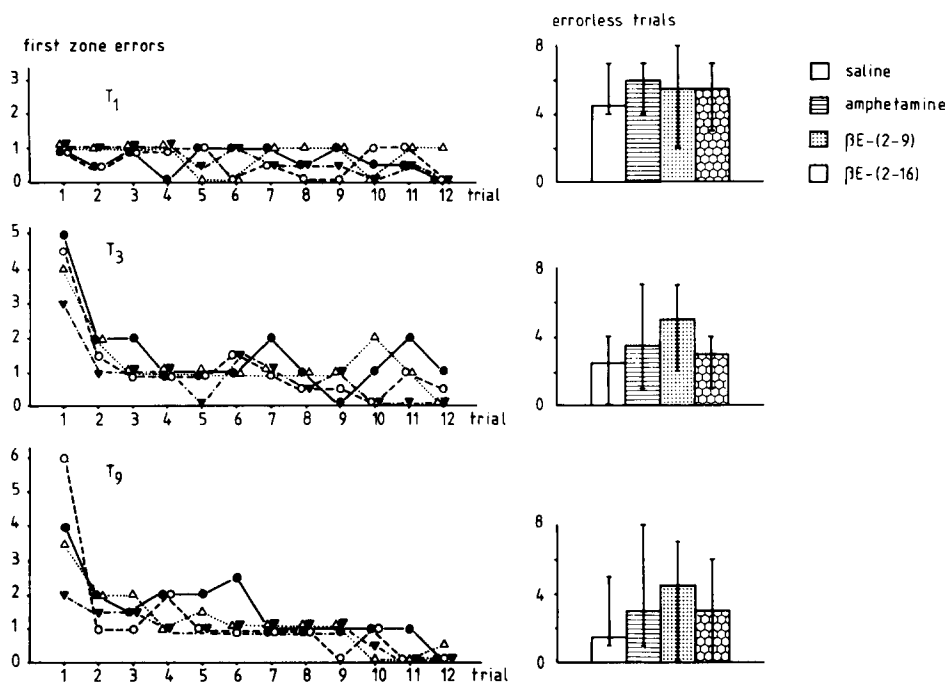


FIG. 2. The median of the number of first zone errors (left) and the median and 95% confidence limits of the total number of errorless trials (right) in each of the three test sessions in Experiment I, after subcutaneous treatment with saline (closed circles), β E-(2-9) (closed triangles, 0.125 mg/kg), β E-(2-16) (open triangles, 0.125 mg/kg) or amphetamine (open circles, 0.45 mg/kg). [Number of rats per group: 10, except for the β E-(2-16) group in T₃ and the amphetamine group in T₉: $n=9$.]

for the contrasts of the control group with each of the three experience groups.

Experimental Procedures

Experiment I. Forty male Wistar rats (body weight on the habituation day 147–187 g, approximate age 7 weeks) were tested subsequently in the configurations T₁, T₃ and T₉ from the Davenport series (see Fig. 1). The experiment was performed in two equally sized replications. Behavioral measures were the number of errorless trials per session and the number of first zone errors in the first trial and summed over 12 trials. Second zone errors were not determined because in a previous study (5) we found no difference in the effects of β E-(2-16) on first and second zone errors.

The animals were distributed over the treatment groups at random per cage, so that each cage contained one animal from each treatment group. Groups of animals were treated with amphetamine (0.45 mg/kg), β E-(2-9) (0.125 mg/kg), β E-(2-16) (0.125 mg/kg) and saline (controls). On the second test day one animal from the β E-(2-16)-treated group and on the third test day one animal from the amphetamine-treated group showed a startle response followed by refusal to run. These animals were discarded from the analysis but only on the mentioned test days.

Experiment II. Once a week a new replication was started, using 160 rats in total (12 \times 12 and 1 \times 16 rats). Their body weight at the start of the experiment was 140–193 g (approximate age 7 weeks). On the first test day the animals were treated and tested in T₉ and T₃₀, then trained further (without injections) in T₂–T₈ of the Davenport series, and again treated and tested in T₃₀ or T₉ on day 9. No animal was tested twice in the same configuration.

On basis of the criteria mentioned for the pretraining procedure, five animals were discarded before the testing phase. The remaining 155 animals were divided in 3 equal classes on basis of their number of trials in P₅ with a running latency ≤ 10 sec at each weekly replication. For the test on day 1 the animals of each class were distributed at random over the four treatment groups [amphetamine (0.45 mg/kg), β E-(2-9) (0.125 mg/kg), β E-(2-16) (0.125 mg/kg), saline]. For the test on day 9 the animals from each treatment group on day 1 were redistributed at random over the four groups in such a way that each treatment group on day 9 contained 25% of the animals from each of the treatment groups on day 1. Two animals were discarded because of an experimenter's error (by accident 10 trials were given to a rat in the amphetamine group tested in T₉ on day 1, therefore only the data of the first trial of this rat were used) and illness (on day 9 one rat was dropped before the test started because of signs of illness), respectively.

For data analysis, data on test day 1 were assumed to be independent from those on test day 9. The raw data of each subexperiment were tested with the Kruskal-Wallis test, in case of significance followed by the Mann-Whitney U-test. In addition, the k-sample test for aligned observations for unequal-sized samples was applied on pooled data of subexperiments aligned on the median of these subexperiments: T₉ (pooled data of day 1 and day 9), T₃₀ (pooled data of day 1 and day 9), day 1 (pooled data of T₉ and T₃₀), day 9 (pooled data of T₉ and T₃₀), pooled data of all four subexperiments. These tests on pooled data served to test if there were differences in effect either between the configurations or between the test days, and if there were overall effects that could not be detected in the (smaller) subexperiments.

In the first test trial in T₉ and T₃₀ data were collected for maximally 600 sec; animals that had not reached the goal within

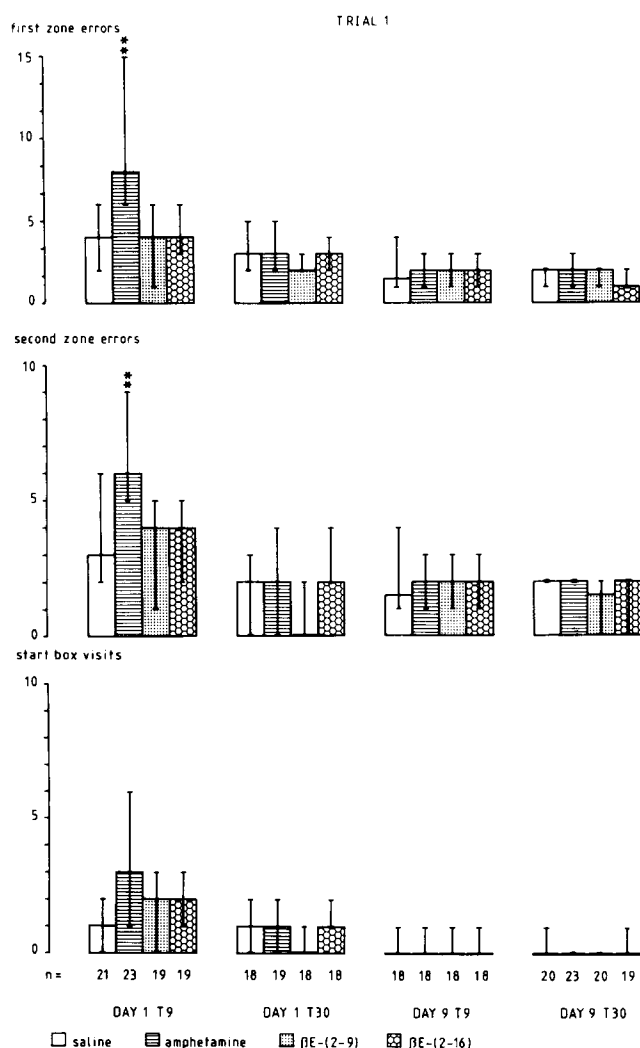


FIG. 3. The effect of subcutaneous administration of amphetamine (0.45 mg/kg), β E-(2-9) (0.125 mg/kg) and β E-(2-16) (0.125 mg/kg), per subexperiment, in Experiment II. Shown are the medians and 95% confidence limits for trial 1. (* $p \leq 0.05$, ** $p \leq 0.01$.)

this time were not tested further in that session. When an animal exceeded a criterion of 300 sec for any of the trials 2-12, its test session was discontinued and only the data of its first trial were used in the analysis. In total, nine rats exceeded these criteria but only on test day 1. Eight of these animals were tested in T9, two of which were treated with saline and the remaining six belonged to the amphetamine-treated group. The ninth animal was tested in T30 and treated with amphetamine.

RESULTS

Experiment I

Figure 2 shows the frequency of the first zone errors in the course of the session and the number of errorless trials for each of the three test sessions. No significant treatment effects were found on these parameters. However, the amphetamine-treated animals showed a slightly higher median number of first zone errors but only in the first trial of T9 (in T9 4 of the 9 rats in the amphetamine-treated group made ≥ 7 first zone errors in the first

TABLE 1
THE SPATIAL DISTRIBUTION OF VISITS TO BLIND ALLEYS IN THE FIRST TRIAL IN T9 ON DAY 1

Number of Visits	Blind Alley	Treatment			
		Saline	Amphetamine	β E-(2-9)	β E-(2-16)
≥ 2	A	81	95	71	83
	C	44	81	36	58
	F	56	56	33	60
	H	0	45	0	0
≥ 4	A	19	50	35	17
	C	13	38	14	5
	F	0	13	0	20
	H	0	0	0	0
≥ 7	A	0	32	6	6
	C	6	14	0	0
	F	0	0	0	0
	H	0	0	0	0

Shown is the number of rats visiting the blind alleys (indicated with the letter of the corresponding first error zones, see Fig. 1) of T9 on day 1 in the first trial ≥ 2 times, ≥ 4 times or ≥ 7 times, expressed as the percentage of the number of rats in each treatment group visiting at least once.

trial, whereas in each of the other three treatment groups only 1 or 2 out of 10 animals had such score).

Experiment II

The data of this experiment are summarized in Figs. 3 (trial 1) and 4 (trials 2-12). The peptides β E-(2-9) and β E-(2-16) did not significantly change the performance of the rats, neither in the first trial, nor in trials 2-12.

In the first trial (Fig. 3), amphetamine treatment resulted in a significantly increased number of first and second zone errors in T9 on day 1 [Kruskal-Wallis test: $H(3) = 14.17$, $p = 0.003$ for first zone errors and $H(3) = 12.54$, $p = 0.006$ for second zone errors, followed by Mann-Whitney U-test: $U = 111.5$, $p = 0.002$ for first zone errors and $U = 127.0$, $p = 0.007$ for second zone errors]. The k-sample test on the data pooled per test day showed a significant increase of first and second zone errors on day 1 ($p \leq 0.05$), but not on day 9, indicating an interaction between the effect and experience level. The k-sample test on the data pooled per configuration showed a significant increase ($p \leq 0.05$) of first and second zone errors and start box visits in T9 but not in T30, suggesting an interaction between the effect and the test configurations. When pooled over both days and configurations the k-sample test showed a significant ($p \leq 0.05$) increase in first zone errors in the amphetamine-treated group. These results suggest that amphetamine can cause a decreased maze performance, but this effect is dependent on maze experience and configuration. This effect of amphetamine can also explain the relatively high number (eight) of rats tested in T9 on day 1 that exceeded the latency criteria. Six belonged to the amphetamine group, two were treated with saline. With the exception of one saline- and one amphetamine-treated rat, all these animals exceeded the 600-sec criterion during the first trial.

In trials 2-12 (Fig. 4), the number of start box visits was significantly decreased in the amphetamine-treated animals in T30 on day 1 [Kruskal-Wallis test: $H(3) = 8.41$, $p = 0.038$, Mann-

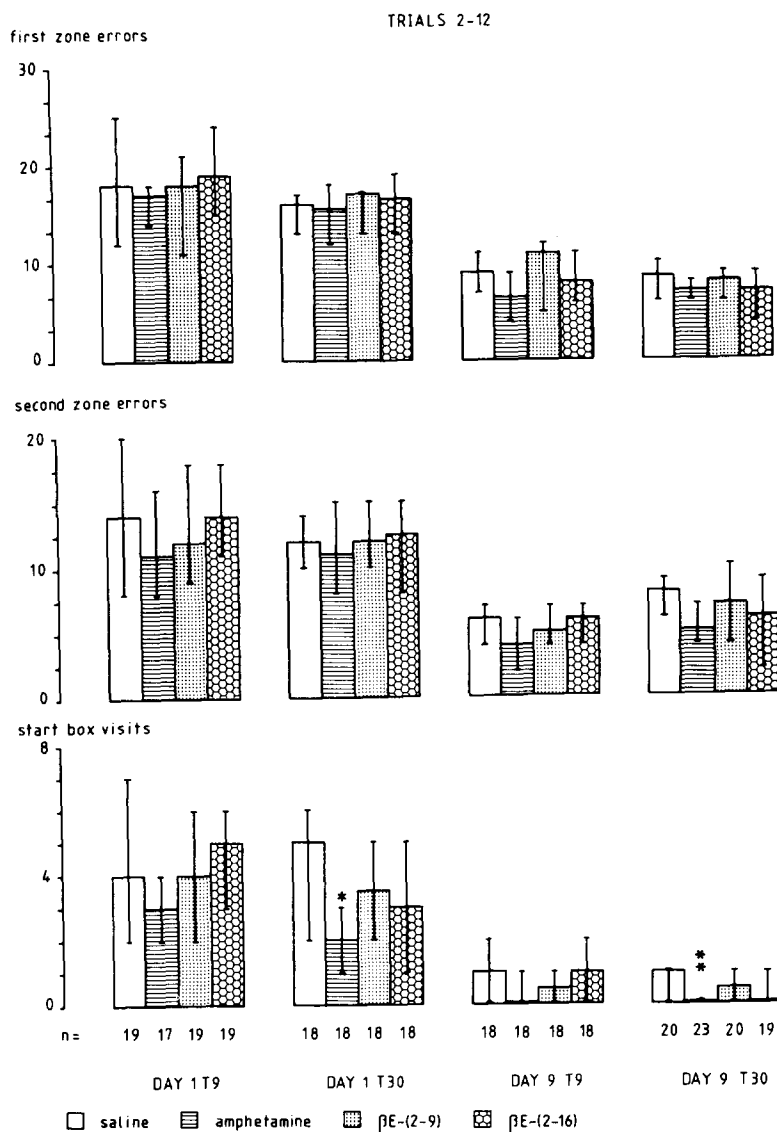


FIG. 4. The effect of subcutaneous administration of amphetamine (0.45 mg/kg), β E-(2-9) (0.125 mg/kg) and β E-(2-16) (0.125 mg/kg), per subexperiment, in Experiment II. Shown are the medians and 95% confidence limits for trials 2-12. (* $p \leq 0.05$, ** $p \leq 0.01$.)

Whitney U-test: $U = 240.0$, $p = 0.013$] as well as on day 9 [Kruskal-Wallis test: $H(3) = 8.17$, $p = 0.043$, Mann-Whitney U-test: $U = 320.5$, $p = 0.008$]. When the data were pooled per test day, a significant decrease of the number of start box visits was found with the k-sample test on both test days ($p \leq 0.05$), and a significant ($p \leq 0.05$) decrease of the number of second zone errors, but only on day 9. When the data were pooled per configuration, the decrease of the number of start box visits was only significant ($p \leq 0.05$) in T30, although also in T9 a slight decrease was present. When pooled over both days and configurations, the k-sample test showed a significant ($p \leq 0.05$) overall decrease of the number of second zone errors and of the number of start box visits. These results suggest that, in addition to the decreased performance (as indicated by an increased number of errors and start box visits) found in the first trial on day 1 in T9, amphetamine can cause an increase in performance (as indicated

by a decrease in errors and start box visits) in trials 2-12 that does not clearly interact with maze configuration or level of experience.

Effects on Initial and Repeated Error Patterns

The error patterns of the different subexperiments did not show clear differences between the experimental groups that could explain the treatment effect reported above, except for the pattern in T9 on day 1. The amphetamine-treated group has a higher percentage of initially visiting rats as compared to the other groups in error zones F, E, H and G of T9 (see Fig. 1) on day 1, but only in the first trial. Repeated errors (percentage of rats visiting at least twice) were increased in the amphetamine-treated group in the same trial in all the error zones. Table 1 shows the number of rats visiting the first error zones of the four blind alleys in trial 1 at least 2, 4 or 7 times, expressed as a percentage of the number of

rats in the treatment group visiting at least once. These percentages are increased in the amphetamine-treated group. Amphetamine caused an increase of the number of rats repeating visits as well as the number of times they repeated. Although the amphetamine-treated rats visit all error zones more frequently, the general spatial pattern of their visits is still comparable to that of the other groups. In Table 1 the gradient over the blind alleys in perseverance percentage that is present in the saline- and peptide-treated rats, is in general also found in the amphetamine-treated rats.

DISCUSSION

No clear effects of the two β -endorphin fragments were found. However, amphetamine increased the number of errors and start box visits in the first trial in T9 in animals with a relatively low level of previous maze running experience. This effect was statistically significant in Experiment II, but a tendency was also present in Experiment I. In trials 2–12, the amphetamine-treated animals performed at least as well or slightly better (a decreased number of errors and start box visits) than the placebo-treated rats. The effect in trials 2–12 was not dependent on configuration or test day. Although the results found in trials 2–12 may have been influenced by removal of those animals exceeding the time criterion in the first trial, the trends in the data for animals tested in T9 were comparable to those of the more complete data obtained in T30 on day 1 and both configurations on day 9. Especially the results from Experiment II suggest that effects of a low dose of amphetamine on rat maze behavior are dependent on experience level of the rats as well as on maze configuration, and that qualitatively different effects can occur within one experiment.

The disruptive effect of amphetamine in the first trial in T9 on day 1 may be related to the well-known stereotyped behavior which can be elicited by amphetamine. Table 1 shows that the amphetamine-treated rats showed the same spatial pattern of errors as placebo-treated controls, but they repeated these errors more often. Amphetamine-induced stereotyped behavior and its dura-

tion are known to be dependent on environmental and other experimental factors (1,17). The expression of the effect of amphetamine in the first trial of T9 in an early phase of the test series may be related to the effort that the rat has to make to find the correct route in the maze. This effort may be higher if the level of experience is lower or if the maze configuration is more difficult. In terms of errors made by saline-treated rats, T9 can hardly be assumed to be more difficult than T30 or T3 (see Figs. 2–4). However, T9 is the only one of these configurations in which part of the correct path shows an angle as large as 90 degrees with the direction that rats probably prefer in these mazes, i.e., the direction corresponding to that of the diagonal from start to goal box (6). For the animals tested on day 1 in T9, this course of the path was new. Amphetamine treatment may have decreased the ability of the animals to adapt their previously successful strategy to the new orientation of the path in T9, but only until they found the goal box for the first time. After having completed the first trial or receiving training in other configurations (some of which have zigzagging routes like T9) on days 2–8, amphetamine does not disrupt their performance anymore.

The slightly improved performance in amphetamine-treated rats shown in trials 2–12 may have been caused by a generally increased learning ability, attention or motivation. The error patterns were not changed clearly in these trials. Increased performance in learning tests after treatment with amphetamine has been found previously by others (13,18).

The fact that no effects were found of the two β -endorphin fragments makes a qualitative comparison of amphetamine and endorphin effects on maze behavior difficult. Therefore, the results do not allow us to draw conclusions with respect to the previously reported similarity in effects of the investigated α -type endorphins and amphetamine. The results of the present experiment and the difference in results between this study and those reported previously (2) suggest that experimental conditions interact with the investigated drug and peptide effects. Further examination of the influence of methodological factors is essential to understand the effects of amphetamine and β -endorphin fragments on rat maze behavior.

REFERENCES

1. Beck, C. H. M.; Chow, H. L.; Cooper, S. J. Initial environment influences amphetamine-induced stereotypy: Subsequently environment change has little effect. *Behav. Neural Biol.* 46:383–397; 1986.
2. Bohus, B. Opiomelanocortins and behavioral adaptation. *Pharmacol. Ther.* 26:417–451; 1984.
3. BMDP statistical software. Berkeley: University of California Press; 1983.
4. Davenport, J. W.; Hagquist, W. W.; Rankin, G. R. The symmetrical maze: An automated closed-field test series for rats. *Behav. Res. Methods Instrum.* 2:112–118; 1970.
5. De Boer, S. Effects of beta-endorphin fragments and amphetamine on problem solving behavior in the rat. Ph.D. Thesis, University of Groningen; 1986:77–110.
6. De Boer, S.; Bohus, B. The spatial distribution of errors made by rats in Hebb-Williams type mazes in relation to the spatial properties of the blind alleys. *Behav. Proc.* 16:137–165; 1988.
7. De Wied, D.; Bohus, B.; Van Ree, J. M.; Urban, I. Behavioral and electrophysiological effects of peptides related to lipotropin (β -LPH). *J. Pharmacol. Exp. Ther.* 204:570–580; 1978.
8. De Wied, D.; Jolles, J. Neuropeptides derived from pro-opiomelanocortin: Behavioral, physiological, and neurochemical effects. *Physiol. Rev.* 62:976–1059; 1982.
9. De Wied, D.; Kovács, G. L.; Bohus, B.; Van Ree, J. M.; Greven, H. M. Neuroleptic activity of the neuropeptide β -LPH_{62–77} ((des-tyr¹)- γ -endorphin; DTyE). *Eur. J. Pharmacol.* 49:427–436; 1978.
10. Greven, H. M.; De Wied, D. Structure and behavioural activity of peptides related to corticotrophin and lipotropin. In: De Wied, D.; Van Keep, P., eds. *Hormones and the brain*. Lancaster: MTP Press Limited; 1980:115–127.
11. Izquierdo, I.; Perry, M. L.; Dias, R. D.; Souza, D. O.; Elisabetsky, E.; Carrasco, M. A.; Orsingher, O. A.; Netto, C. A. Endogenous opioids, memory modulation, and state dependency. In: Martinez, J. L.; Jensen, R. A.; Messing, R. B.; Riger, H.; McGaugh, J. L., eds. *Endogenous peptides and learning and memory processes*. New York: Academic Press; 1981:269–289.
12. Kastin, A. J.; Mauk, M. D.; Schally, A. V.; Coy, D. H. Unusual dose-related effect of an endorphin analog in a complex maze. *Physiol. Behav.* 25:959–962; 1980.
13. Kovács, G. L.; De Wied, D. Effects of amphetamine and haloperidol on avoidance behavior and exploratory activity. *Eur. J. Pharmacol.* 53:103–107; 1978.
14. Marascuilo, L. A.; McSweeney, M. Nonparametric and distribution-free methods for the social sciences. Monterey, CA: Brooks/Cole Publishing Company; 1977:410–414.
15. Meyerson, B. J. Comparison of the effects of β -endorphin and morphine on exploratory and socio-sexual behaviour in the male rat. *Eur. J. Pharmacol.* 69:453–463; 1981.
16. Rabinovitch, M. S.; Rosvold, H. E. A closed-field intelligence test for rats. *Can. J. Psychol.* 5:122–128; 1951.
17. Rebec, G. V.; Bashore, T. R. Critical issues in assessing the behavioral effects of amphetamine. *Neurosci. Biobehav. Rev.* 8: 153–159; 1984.
18. Sara, S. J.; Deweer, B. Memory retrieval enhanced by amphetamine after a long retention interval. *Behav. Neural Biol.* 36:146–160; 1982.

19. Van Ree, J. M.; Bohus, B.; De Wied, D. Similarity between behavioral effects of des-tyrosine- γ -endorphin and haloperidol and of α -endorphin and amphetamine. In: Leong Way, E., ed. Endogenous and exogenous opiate agonists and antagonists. New York: Pergamon; 1980:459–462.
20. Van Ree, J. M.; De Wied, D. Behavioral effects of the α -endorphin fragment 2–9. *Life Sci.* 31:2383–2386; 1982.
21. Van Ree, J. M.; Verhoeven, W. M. A.; De Wied, D. Animal and clinical research on neuropeptides and schizophrenia. *Prog. Brain Res.* 72:249–267; 1987.